Incidence and severity of childhood pneumonia in the first year of life in a South African birth cohort: the Drakenstein Child Health Study

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Summary

Background Childhood pneumonia causes substantial mortality and morbidity. Accurate measurements of pneumonia incidence are scarce in low-income and middle-income countries, particularly after implementation of pneumococcal conjugate vaccine. We aimed to assess the incidence, severity, and risk factors for pneumonia in the first year of life in children enrolled in a South African birth cohort.

Methods This birth cohort study is being done at two sites in Paarl, a periurban area of South Africa. We enrolled pregnant women (>18 years) and followed up mother–infant pairs to 1 year of age. We obtained data for risk factors and respiratory symptoms. Children received 13-valent pneumococcal conjugate vaccine according to national immunisation schedules. We established pneumonia surveillance systems and documented episodes of ambulatory pneumonia and pneumonia warranting hospital admission. We calculated incidence rate ratios for pneumonia with mixed-effects Poisson regression.

Findings Between May 29, 2012 and May 31, 2014, we enrolled 697 infants who accrued 513 child-years of follow-up. We recorded 141 pneumonia episodes, with an incidence of 0·27 episodes per child-year (95% CI 0·23–0·32). 32 (23%) pneumonia cases were severe pneumonia, with an incidence of 0·06 episodes per child-year (95% CI 0·04–0·08). Two (1%) of 141 pneumonia episodes led to death from pneumonia. Maternal HIV, maternal smoking, male sex, and malnutrition were associated with an increased incidence of pneumonia.

Interpretation Pneumonia incidence was high in the first year of life, despite a strong immunisation programme including 13-valent pneumococcal conjugate vaccine. Incidence was associated with pneumonia risk factors that are amenable to interventions. Prevention of childhood pneumonia through public health interventions to address these risk factors should be strengthened.

Funding Bill & Melinda Gates Foundation, South African Thoracic Society, Federation of Infectious Diseases Societies of South Africa, and University of Cape Town.

Lancet Glob Health 2015; 3: e95–103

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Introduction

Pneumonia is the leading cause of death in children, accounting for about 17% of 6·3 million child deaths in 2010—more than HIV, measles, and malaria combined.[1,2] Pneumonia also contributes substantially to health-care use in childhood, with an estimated 120 million episodes annually.[3] The burden of pneumonia is disproportionately high in African children, with 36 million pneumonia cases and 600 000 pneumonia-associated deaths annually.[3] Chronic respiratory complications such as bronchiectasis frequently arise after childhood pneumonia, in up to 13% of children admitted to hospital.[4] As such, understanding of the incidence and severity of pneumonia is important to identify preventive interventions, plan health systems, and make projections of burden of disease.

Longitudinal community-based studies with reliable measurements of pneumonia incidence are rare in low-income and middle-income countries.[5] Estimates of pneumonia incidence have therefore been modelled on the basis of previous incidence and risk-factor prevalence. The most recent global estimate of pneumonia incidence in children younger than 5 years from low-income and middle-income countries was 0·22 episodes per child-year, with 11·5% of cases meeting criteria for severe disease. The country-specific estimate for South Africa was 0·14 episodes per child-year, with 11·1% of cases defined as severe.[6]

Randomised controlled trials of pneumococcal conjugate vaccination, using 7-valent or 9-valent vaccine, reported substantial decreases in the incidence of clinical or radiologically confirmed pneumonia, and hospital admissions for pneumonia.[7–11] After introduction of the 7-valent vaccine, then the 10-valent and 13-valent vaccines, into national immunisation programmes, substantial reductions in the incidence and severity of childhood pneumonia were reported in high-income countries,[12–15] and in Uruguay[16] and Brazil.[17] However, data for sub-Saharan Africa are scarce, despite the continent's substantial burden of childhood pneumonia and high incidence of severe disease.

The South African Expanded Program On Immunisation recommends four doses of a five-vaccine combination (diphtheria, tetanus, acellular pertussis, *Haemophilus influenzae* type b, and inactivated polio vaccine) given at the ages of 6, 10, and 14 weeks, and 18 months, and measles vaccine at 9 and 18 months of age. 7-valent pneumococcal vaccination was introduced in April, 2009, with a novel schedule (6 weeks, 14 weeks, and 9 months, with no catch-up doses given); this vaccine was replaced with the 13-valent formulation in June, 2011.[18] From February to May, 2012, children aged 18–35 months received a catch-up dose of the 13-valent vaccine.

	TC Newman clinic (n=359)	Mbekweni clinic (n=338)
Maternal characteristics		
Race and ethnic origin		
Black African	5 (1%)	337 (99%)
Mixed race	354 (99%)	1 (<1%)
In formal employment	109 (30%)	69 (20%)
Receives national child support grant	200 (56%)	188 (56%)
Lives in formal housing	266 (74%)	182 (54%)
Household crowding		
Three or fewer people	79 (22%)	145 (43%)
Four or five people	138 (39%)	106 (31%)
More than five people	141 (39%)	86 (26%)
Missing data	1 (<1%)	1 (<1%)
Education		
Primary school only	25 (7%)	35 (10%)
Some secondary school	179 (50%)	182 (54%)
Finished secondary school	155 (43%)	120 (36%)
Missing data	0	1 (<1%)
Socioeconomic status quartile		
Lowest	52 (14%)	107 (32%)
Moderately low	96 (27%)	106 (31%)
Moderately high	88 (25%)	73 (22%)
Highest	123 (34%)	51 (15%)
Missing data	0	1 (<1%)
HIV infected	9 (2%)	121 (36%)
Self-reported smoker	162 (45%)	14 (4%)
Infant characteristics		
Sex		
Male	206 (57%)	166 (49%)
Female	153 (43%)	172 (51%)
Preterm (<37 weeks)	52 (15%)	44 (13%)
Low birthweight (<2500 g)	70 (20%)	38 (11%)
Birthweight (kg)	2·99 (2·59–3·40)	3·12 (2·77–3·45)
Z score		
Weight-for-age	−0·45 (−1·33 to 0·25)	−0·30 (−1·0 to 0·43)
Height-for-age	−0·68 (−1·67 to 0·1)	−0·18 (−1·26 to 0·59)
Feeding choice		
Never breastfed	31 (9%)	105 (31%)
Exclusively breastfed for 6 months*	21/231 (9%)	27/216 (13%)
Mixed feeding at 6 months*	139/231 (60%)	66/216 (31%)
Exclusive formula feeding at 6 months*	71/231 (31%)	123/216 (57%)
Age at censoring (days)	358 (186–365)	308 (166–365)
Vaccination coverage		
All primary series doses given on time	196/329 (60%)	206/308 (67%)
All primary series doses given, some doses late	54/329 (16%)	73/308 (24%)
At least one primary series dose missed	79/329 (24%)	29/308 (9%)

Data are n (%), median (IQR), or n/N (%). *Data for participants with completed 6-month feeding questionnaires.

***Table 1*: Baseline characteristics**

The Drakenstein Child Health Study is investigating the incidence and long-term consequences of childhood pneumonia in a South African birth cohort. We examined the incidence and severity of early-life pneumonia in this setting, and associations involving established sociodemographic, clinical, and behavioural risk factors for childhood pneumonia.

Methods

Study design and participants

This birth cohort study being done at two sites in Paarl, a periurban area 60 km outside Cape Town, South Africa.[19] Study sites were in two clinics (TC Newman and Mbekweni) roughly 5 km apart and serving two separate communities with a combined population of about 200 000 people. Residents of both areas have low socioeconomic status, but are ethnically, linguistically, and culturally heterogeneous. The TC Newman clinic serves a population composed of mostly Afrikaans-speaking, mixed-race individuals; the Mbekweni clinic's population is mainly isiXhosa-speaking black Africans.[19]

We enrolled pregnant women who were between 20 and 28 weeks' gestation and attending antenatal care at one of the two clinics; we followed up women through pregnancy and childbirth. Exclusion criteria were age younger than 18 years and intention to leave the area within 1 year.

Ethics approval was obtained from the University of Cape Town Faculty of Health Sciences Human Research Ethics Committee (Human Research Ethics committee reference numbers 401/2009 and 651/2013) and the Provincial Child Health Research committee. Mothers provided written informed consent at enrolment.

Procedures

Questionnaires about maternal health were administered and we obtained antenatal data. Obstetric care was provided at Paarl Hospital where all births took place. Detailed birth information was obtained at the time of delivery. Infant follow-up visits were at 6, 10, and 14 weeks old, and 6, 9, and 12 months old.[19] Trained study nurses did interviews in the mother's home language. Data for environmental exposures, pneumonia risk factors, anthropometry, and the child's respiratory symptoms were obtained at scheduled visits. Missed visits were rebooked with a study mobile phone network system or by study community-based fieldworkers.

Mothers were counselled about respiratory symptoms at every visit and advised to attend the study site or contact study staff whenever the child developed cough or

difficulty breathing, in addition to scheduled study visits. Study nurses were trained to diagnose pneumonia or severe pneumonia according to WHO clinical case definitions.[20] Pneumonia was diagnosed in children with cough or difficulty breathing and age-specific tachypnoea (≥50 breaths per min for children aged 2–12 months) or if the child had lower chest wall indrawing. Severe pneumonia was diagnosed in children younger than 2 months with tachypnoea (>60 breaths per min) or lower chest wall indrawing, or in children of any age if the child had a general danger sign (ie, cyanosed, unable to drink, seizures, or decreased level of consciousness).[20] The treating doctor made the decision to admit a child to hospital; indications included severe pneumonia, hypoxia (oxygen saturation of ≤92% in room air), or poor social circumstances in which ambulatory treatment was not feasible. Events that happened more than 14 days after admission or a previous event were considered to be new-onset, community-acquired pneumonia.

An active surveillance system was established to detect participants with pneumonia or severe pneumonia. Study staff undertook pneumonia surveillance at primary care clinics and at Paarl Hospital on weekdays during working hours (0800–1600 h); surveillance continued at Paarl Hospital after hours and over weekends when clinics were closed. If a participant attended a primary health-care clinic or the emergency unit at Paarl Hospital, the health-care provider could contact the study nurse on the 24 h mobile phone number. Mothers were given the mobile phone number to enable them to contact the study nurse on call if their child became ill. The study doctor provided regular training for all primary health-care nurses in the accurate assessment of symptoms and signs in young children, and to ensure birth cohort participants were referred to the research study site when pneumonia or severe pneumonia was diagnosed.

Statistical analysis

The overall sample size for the study was 1000 mother–infant pairs to provide at least 550 pneumonia episodes; this preliminary analysis was completed after 500 child-years of follow-up had been accrued to assess pneumonia incidence with precision of plus or minus 0·05 cases per child-year. On the basis of vaccine studies, we expected the incidence of clinically defined pneumonia or severe pneumonia to be roughly 10% lower in this vaccinated cohort than pneumonia incidence estimates reported before the introduction of pneumococcal conjugate vaccine. We also expected significant associations of pneumonia with maternal smoking status, household crowding, low birthweight, and suboptimum breastfeeding.

For exploratory data analysis, we summarised continuous variables as medians with IQRs and categorical variables as percentages with 95% CIs. We compared medians with rank-sum tests and proportions with χ^2 tests. We derived Z scores from WHO child growth standards[21] at birth and at every follow-up visit; we used the median of all the weight-for-age Z scores for each child to summarise nutrition status over the duration of follow-up. Children were considered severely underweight or stunted if weight-for-age and length-for-age Z scores were less than –2. Follow-up was censored at last visit seen, death, or 1 year of age. We divided observation of each child into 1 month intervals, with 6299 intervals clustered around 697 infants. We analysed factors associated with pneumonia events for the whole cohort and by study site. For multivariable modelling of pneumonia incidence we used mixed-effect Poisson models, including a random intercept for each infant; results are presented as incidence rate ratios with 95% CIs. Because weight-for-age Z scores are likely to be a causal intermediate through which different risk factors affect pneumonia risk, we developed separate models to include weight-for-age Z score. In comparisons of seasonal incidence we categorised December to February as summer, March to May as autumn, June to August as winter, and September to November as spring. We did analyses with Stata (version 11).

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between May 29, 2012 and May 31, 2014, we enrolled 697 infants who accrued 513 child-years of follow up (appendix). In the first year of life, 13 (2%) infants died,

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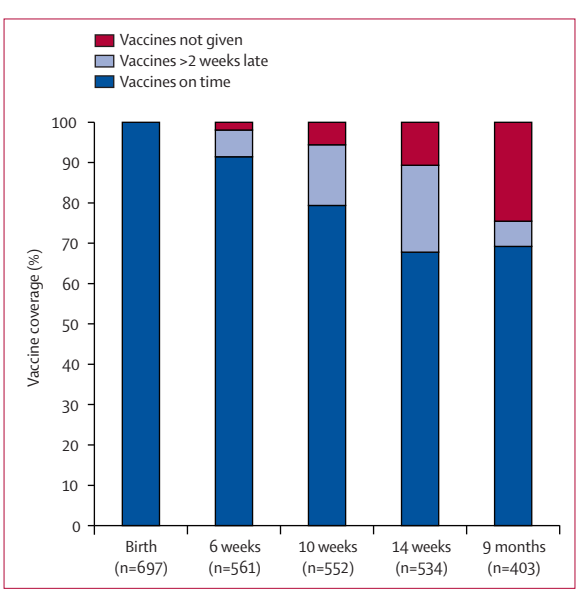

Figure 1: **Coverage of routine childhood vaccinations throughout the first year of life**
Haemophilus influenzae type b conjugate vaccine at 6, 10, and 14 weeks, and pneumococcal conjugate vaccine at 6 weeks, 14 weeks, and 9 months.

	Pneumonia events (n=141)	Person-time (years)	Incidence of pneumonia (95% CI; episodes per child-year)	Incidence rate ratio (95% CI)
Study site				
Mbekweni	55 (39%)	245·0	0·22 (0·17–0·29)	1
TC Newman	86 (61%)	267·8	0·32 (0·26–0·40)	1·43 (1·01–2·04)
Season				
Summer	14 (10%)	130·7	0·11 (0·06–0·18)	1
Autumn	39 (28%)	148·7	0·26 (0·19–0·36)	2·45 (1·30–4·88)
Winter	47 (33%)	102·5	0·45 (0·34–0·61)	4·28 (2·31–8·42)
Spring	41 (29%)	118·1	0·35 (0·25–0·47)	3·24 (1·73–6·44)
Smoking status of mother				
Non-smoker	87 (62%)	378·1	0·23 (0·18–0·28)	1
Self-reported smoker	54 (38%)	133·0	0·41 (0·30–0·53)	1·76 (1·23–2·50)
Maternal education				
Primary school only	27 (19%)	45·2	0·60 (0·39–0·87)	1
Some secondary	74 (53%)	266·7	0·27 (0·22–0·35)	0·46 (0·30–0·75)
Completed secondary	40 (28%)	199·9	0·20 (0·14–0·27)	0·33 (0·20–0·57)
Sex				
Female	44 (31%)	245·4	0·18 (0·13–0·24)	1
Male	97 (69%)	267·4	0·36 (0·29–0·44)	2·02 (1·40–2·96)
Child's HIV exposure				
Not exposed	106 (75%)	413·8	0·26 (0·21–0·31)	1
Exposed*	35 (25%)	99·0	0·35 (0·25–0·49)	1·38 (0·91–2·03)
Child age (months)				
<1	7 (5%)	58·2	0·12 (0·05–0·25)	1
1–6	106 (75%)	292·9	0·36 (0·30–0·44)	3·00 (1·41–7·67)
6–12	28 (20%)	161·7	0·17 (0·12 - 0·26)	1·44 (0·61–3·90)
Term				
Full term	96 (68%)	392·53	0·24 (0·20–0·30)	1
Preterm (<37 weeks)	54 (38%)	120·28	0·37 (0·27–0·50)	1·52 (1·04–2·20)
Birthweight (g)				
≥2500	110 (78%)	430·18	0·26 (0·21–0·31)	1
<2500	31 (22%)	82·62	0·38 (0·25–0·54)	1·47 (0·95–2·20)
***Z* score**				
Weight-for-age >–2	115 (82%)	466·1	0·25 (0·20–0·30)	1
Weight-for-age <–2	26 (18%)	46·7	0·55 (0·36–0·82)	2·25 (1·41–3·48)
Length-for-age >–2	104 (74%)	426·5	0·24 (0·20–0·30)	1
Length-for-age <–2	37 (26%)	86·3	0·43 (0·30–0·59)	1·76 (1·17–2·58)
Feeding				
Exclusively breastfed for 6 months	8 (6%)	44·57	0·18 (0·07–0·35)	1
Any formula milk before 6 months	133 (94%)	468·0	0·28 (0·24–0·34)	1·58 (0·78–3·75)
Doses of pneumococcal conjugate vaccine†				
Age 6–14 weeks				
First dose not given	1	2·04	0·50 (0·01–2·77)	1
First dose given on time	44	86·72	0·51 (0·37–0·68)	1·04 (0·18–41·8)
Age >14 weeks				
Second dose not given	7	19·82	0·35 (0·14–0·73)	1
Second and third doses on time	61	276·49	0·22 (0·17–0·28)	0·62 (0·29–1·62)

Data are n (%), unless otherwise indicated. *All HIV-exposed children were HIV-uninfected. †Out of a total number of pneumonia events of 113 (28 events occurred before age 6 weeks, which is when the first dose of vaccine is due).

Table 2: **Incidence of pneumonia in the cohort, by maternal and infant characteristics**

and 89 (13%) were disenrolled (12 mothers withdrew consent, 51 relocated, 17 were unable to be contacted, and nine disenrolled for other reasons). Of the 595 children still in follow-up on May 31, 2014, 309 (52%) were 1 year or older, and 286 (48%) were younger than 1 year. Most children who were disenrolled remained in follow-up and in contact with the study staff until the date of termination, so their health outcomes are known. We recorded differences in baseline characteristics of mothers and infants between the two enrolment sites (table 1). Exposure to environmental tobacco smoke was common: a quarter of mothers self-reported smoking, with higher rates at TC Newman than Mbekweni (table 1), whereas 439 (63%) children were reported to share a household with at least one cigarette smoker. Median birthweight and infant nutritional status were lower at TC Newman than Mbekweni (table 1). Roughly a fifth of mothers were HIV-infected, with higher prevalence at Mbekweni than TC Newman (table 1); no infants were HIV infected. Although 616 (88%) mothers started breastfeeding, only 163 (31%) of 519 were exclusively breastfeeding by 4 months, and 48 (11%) of 447 by 6 months (table 1).

We recorded high immunisation coverage of primary series vaccinations: 512 (98%) of 561 infants received a 6-week vaccine, 521 (94%) of 552 received a 10-week vaccine, and 477 (89%) of 534 received a 14-week vaccine; however, these vaccines were delayed by more than 2 weeks in 37 (7%), 83 (15%), and 115 (22%) infants, respectively (figure 1). Coverage of 9-month vaccination was lower than coverage of earlier vaccinations, with 304 (75%) of 403 children receiving a vaccination at 9 months; 25 (6%) 9-month vaccines were given late (figure 1).

165 episodes met the clinical case definition of pneumonia. 24 (14%) episodes took place on the first day of life. In 18 (11%) babies, tachypnoea and respiratory distress were due to preterm delivery and were treated with nasal continuous positive airway pressure; nine (5%) infants also needed surfactant therapy. Other causes of respiratory distress on the first day of life were congenital pneumonia in two babies, and one congenital diaphragmatic hernia. With exclusion of the 24 events that arose on the first day of life, we recorded 141 episodes of community-acquired pneumonia during the first year (table 2), an incidence of 0·27 episodes per child-year (95% CI 0·23–0·32). These 141 episodes were in 109 children; 22 children had two episodes, nine children had three episodes, and one child had four episodes. In four (3%) episodes, we noted improvement in tachypnoea after bronchodilator administration. We recorded seven cases of community-acquired pneumonia in the first month of life (table 2). Incidence of community-acquired pneumonia from the second month to 1 year of age was 0·29 episodes per child-year (95% CI 0·25–0·35). Incidence was lowest in the first month, highest in the third month, and decreased to 0·24 episodes per child-year in the 12th month (figure 2). Pneumonia incidence in winter was four times higher than in summer (table 2).

32 (23%) events of community-acquired pneumonia met WHO criteria for severe pneumonia; the incidence of severe pneumonia was 0·06 episodes per child-year (95% CI 0·04–0·08). 26 (81%) severe episodes were in the first 2 months of life; 21 (81%) of these infants had lower chest wall indrawing. In this cohort of young infants, WHO severe pneumonia did not correlate well with hypoxia: ten of 32 infants who met the criteria for severe pneumonia had oxygen saturations of less than 92%, with a similar proportion in those younger than 2 months (eight of 26 infants) and those older than that age (two of six infants). Furthermore, only 13 of 23 children with documented hypoxia met criteria for severe pneumonia.

86 (61%) events of community-acquired pneumonia were managed with outpatient care and 55 (39%) events warranted hospital admission. Children admitted to hospital with pneumonia were younger than those with ambulatory pneumonia, had higher median respiratory rates, lower median oxygen saturations, and lower weight-for-age and height-for-age *Z* scores (table 3). Wheeze was present in 65% of pneumonia cases (table 3), but was less common at the time of severe pneumonia (14 [44%] of 32 events) than the time of pneumonia (78 [72%] of 109; p=0·004). Wheeze was present in 82 (71%) of 115 infants older than 2 months, compared with ten (37%) of 26 infants younger than 2 months (p=0·001).

Median length of hospital admission was 3 days (IQR 2–5). We recorded two pneumonia-related deaths, giving a case-fatality ratio of 1·4% (95% CI 0·1–5·0) of all 141 cases of community-acquired pneumonia or 6% (0·7–21) of all 32 severe cases. The first death was of a 3-week-old child with pneumococcal septicaemia and empyema; the second was of a 6-week-old child with a congenital cardiac lesion who died en route to hospital. Both children died before their first pneumococcal conjugate vaccine; post-mortem examinations could not be obtained.

Preterm delivery, severe underweight, and severe stunting were positively associated with incidence of pneumonia, whereas higher maternal educational achievement was negatively associated with incidence (table 2). Few pneumonia events took place in children with missed or delayed vaccinations (table 2). Children older than 14 weeks with a delayed second dose of pneumococcal conjugate vaccine had an increased incidence of pneumonia compared with those who received vaccinations on time, but this association was not statistically significant (table 2).

In multivariable analysis, age, male sex, maternal HIV status, and self-reported smoking were the strongest risk factors for pneumonia (table 4). Breastfeeding duration was not significant in the adjusted model, but was included as a known pneumonia risk factor. When weight-for-age *Z* score was included in the model as a potential causal intermediate, it was strongly associated with pneumonia incidence, and associations involving other risk factors were attenuated (table 4). HIV exposure and young age were the strongest risk factors for severe pneumonia (table 4).

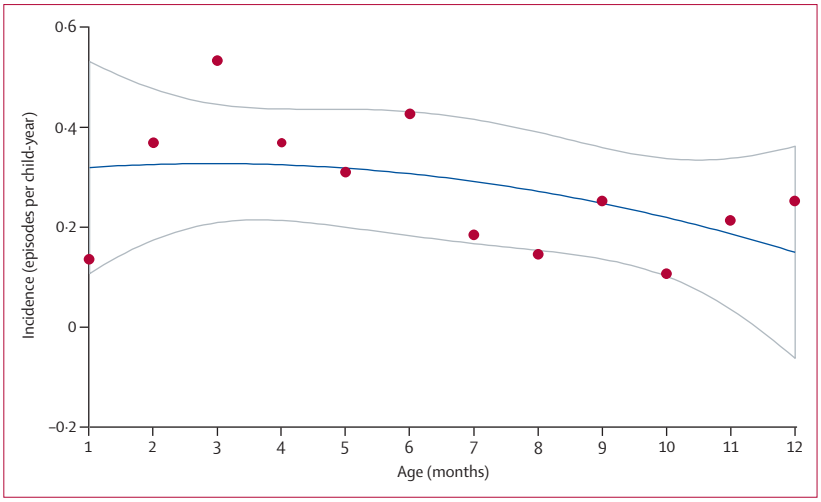

Figure 2: **Incidence of pneumonia during the first year of life**
Red dots show incidence. Blue line shows fitted values. Grey line shows 95% CIs.

	Cases of ambulatory pneumonia (n=86)	Pneumonia cases admitted to hospital (n=55)	p value
Age (months)	4·52 (2·79–5·87)	2·49 (1·57–6·62)	0·01
HIV exposed	19 (22%)	16 (29%)	0·35
Preterm (<37 weeks)	12 (14%)	15 (27%)	0·05
Low birthweight (<2500 g)	16 (19%)	15 (27%)	0·23
Maternal self-reported smoking	32 (37%)	22 (40	0·74
Four or more people in the house	62 (72%)	46 (83%)	0·11
Socioeconomic status quartile			0·47
Lowest	23 (27%)	19 (35%)	..
Moderately low	30 (35%)	13 (24%)	..
Moderately high	19 (22%)	15 (27%)	..
Highest	14 (16%)	8 (15%)	..
Feeding choice			
Exclusively breastfed for 6 months	3 (3%)	5 (9%)	0·30
Mixed feeding	64 (74%)	36 (65%)	..
Never breastfed	19 (22%)	14 (25%)	..
Clinical features			
WHO severe pneumonia	12 (14%)	20 (36%)	0·002
Weight-for-age *Z* score	−0·2 (−1·2 to 0·55)	−1·1 (−1·81 to 0·14)	0·003
Height-for-age *Z* score	−0·69 (-2·1 to 0·54)	−2·2 (−4·1 to 0·02)	0·002
Respiratory rate (breaths per min)	56 (52–62)	62 (56–68)	0·002
Lower chest wall indrawing	36 (42%)	45 (81%)	<0·0001
Wheeze	58 (67%)	34 (62%)	0·49
Fever (>38°C)	17 (24%)	26 (49%)	0·004
Unable to feed	7 (8%)	12 (22%)	0·03
Oxygen saturation (lowest)	97% (94–98)	94% (90–96)	0·001

Data are median (IQR) or n (%).

Table 3: **Risk factors for and clinical features of infants with ambulatory pneumonia or pneumonia needing hospital admission**

	Severe pneumonia	Pneumonia	All pneumonia events (model A)	All pneumonia events (model B)
Male sex	1·20 (0·55–2·62)	2·49 (1·52–4·08)	2·07 (1·37–3·11)	1·98 (1·32–2·99)
HIV exposed	4·04 (1·51–10·80)	1·55 (0·81–2·96)	1·62 (1·01–2·61)	1·52 (0·98–2·36)
Maternal smoking	0·71 (0·28–1·79)	2·36 (1·45–3·82)	1·98 (1·33–2·95)	1·94 (1·32–2·83)
Any formula feeding before age 6 months	0·97 (0·23–4·12)	2·07 (0·70–6·17)	1·74 (0·72–4·20)	1·75 (0·73–4·14)
Child age (1 month units)	0·66 (0·54–0·80)	0·98 (0·92–1·03)	0·93 (0·89–0·98)	0·93 (0·88–0·98)
Weight-for-age *Z* score <–2	..	..	..	1·79 (1·05–3·02)

Data are incidence rate ratio (95% CI). We adjusted all models for site of enrolment. Model A includes risk factors shown and Model B includes risk factors shown and weight-for-age *Z* score as an intermediate variable through which risk factors might affect pneumonia risk.

Table 4: **Incidence rate ratios for severe pneumonia, pneumonia, and total pneumonia events**

Discussion

This birth cohort study provides one of the first measurements of the incidence of pneumonia in infants after introduction of 13-valent pneumococcal conjugate vaccine in a low-income to middle-income setting. We recorded a high incidence of pneumonia during the first year of life, and a high proportion of these cases were severe or warranted hospital admission. This incidence resulted despite high immunisation coverage and a strong primary health-care programme with effective prevention of vertical HIV transmission. The incidence of pneumonia in our study (0·32 episodes per child-year) is more than double the estimated incidence for South African children younger than 5 years (0·14 episodes per child-year) and higher than the median estimate in developing countries of 0·22 episodes per child-year,[6] both of which were calculated before implementation of pneumococcal conjugate vaccine. The higher than expected incidence might be due, in part, to the young age of the cohort, because pneumonia incidence is highest in the first year of life.[22] Moreover, the incidence of pneumonia was highest in infants younger than 6 months, which shows the increased vulnerability of young children to pneumonia and severe pneumonia. The incidence was also substantially higher than that described in the first year of life in high-income countries, which ranges from 0·006 to 0·085 episodes per child-year.[23] However, our incidence is similar to that described in some other low-income and middle-income settings in the first year of life, which might signify differences in populations, diagnostic certainty, or risk factors for pneumonia.[24-26]

The high incidence of pneumonia took place despite high immunisation coverage, including 13-valent pneumococcal conjugate vaccine, acellular pertussis, *Haemophilus influenzae* type b conjugate, and measles vaccines. Delayed vaccination can increase vulnerability to pneumonia because of low protective immunity.[27,28] This study was not designed to assess the effectiveness of increased numbers of vaccine doses; vaccine coverage was high, and few pneumonia events took place in children with missed or delayed vaccinations. For optimum protection against pneumonia, completion of a pneumococcal vaccine series of two primary doses plus one booster dose is needed.[29,30] In support of this finding, the incidence of pneumonia was lower in children who had received two or three immunisations than in those who had received one dose. However, young age might be a confounding variable because children with fewer immunisation doses were younger than those who had completed a primary series.

Despite the young age of the cohort, case-fatality ratios for overall pneumonia cases and for severe pneumonia cases were lower than the global average for children younger than 5 years with severe pneumonia.[3] This finding is probably a result of high immunisation coverage (reducing the severity of pneumonia); good access to health care by birth cohort participants; and a strong primary health-care programme, ensuring timely availability of antibiotic therapy and oxygen at community clinics and referral to hospital when needed.

Known risk factors for pneumonia were confirmed in this cohort and the magnitude of their effects was quantified in the context of a strong primary health-care programme. No child was HIV infected, despite a high prevalence of HIV infection in pregnant women, showing the strong effect of prevention of mother-to-child-transmission programmes. However, exposure to HIV was a significant independent risk factor for pneumonia, especially for severe pneumonia, even after adjustment for feeding choice. This finding could be due to developmental abnormalities of the innate[31] or adaptive[32] immune systems, limited protection due to compromised maternal antibodies, or increased exposure to infectious diseases from living in a household with a member who is HIV infected. This finding draws attention to a group of children who, although maybe not HIV infected, might be especially vulnerable to the development of severe disease. Boys had a higher incidence of pneumonia than girls, possibly because of differences in intrinsic immune or inflammatory responses,[33,34] or differences in lung structure or function.[35] Maternal smoking was associated with increased pneumonia incidence; possible mechanisms include in-utero effects of maternal smoking, which reduces infants' lung growth,[36] or postnatal exposure to tobacco smoke predisposing to respiratory infection or development of wheezing illness.[37] Higher maternal education was significantly associated with decreased incidence of pneumonia, suggesting that maternal education can have a direct effect on child health.

Exclusive breastfeeding for 6 months is recommended for the reduction of pneumonia incidence and mortality in low-income and middle-income settings.[38] Similar to findings from a study in sub-Saharan Africa,[39] a low proportion of participants sustained exclusive breastfeeding for 6 months. The incidence rate ratio from

the Poisson regression suggests that suboptimum breastfeeding is associated with a 70% increased incidence of pneumonia; however, this finding was not significant.

Preterm delivery and low birthweight are recognised risk factors for pneumonia.[40] In our study, severe underweight and severe stunting—both markers of low birthweight and postnatal growth and nutrition—were strongly associated with increased pneumonia incidence. This finding is in line with the well described association of malnutrition with pneumonia incidence and severity,[41] possibly due to impaired immunity or micronutrient deficiency. Further study of the nutritional factors associated with pneumonia risk in this cohort is underway.

Wheezing was common in children with pneumonia. This finding is not unexpected because previous studies of children with pneumonia, including an analysis of more than 4000 episodes of hospital admission for lower respiratory tract infection in young South African children enrolled in a vaccine study, reported concomitant wheezing in about 50% of children who met WHO's clinical case definition of pneumonia.[42–45] The high incidence of wheezing might suggest that viral infection (alone or with other pathogens) is the cause of pneumonia, or that the small airways of young children are especially prone to obstruction due to infection or resulting inflammation. Further study of the bacterial and viral pathogens associated with pneumonia episodes is underway. Because we aimed to report findings for all-cause pneumonia, we included children with wheezing who met the WHO clinical case definition for pneumonia. Moreover, existing evidence shows that viral illness, such as that produced by respiratory syncytial virus, constitutes a large global burden with a substantial case-fatality rate, especially in low-income and middle-income countries.[46] Although distinguishing of bronchiolitis from pneumonia is not possible with WHO case definitions, this infection represents a range of lower respiratory tract illnesses with substantial morbidity and mortality.

Limitations of this study include the possibility of misclassification of pneumonia cases because of differing clinical case definitions.[6] To reduce misclassification, we used standard, recently revised WHO clinical case definitions to enable standardised diagnosis and comparison with other data and research of pneumonia incidence. These case definitions were designed for maximum sensitivity for pneumonia diagnosis, but have lower specificity than other measures such as radiological pneumonia. A strength of this study is the consistent use of such case definitions by study staff. Although use of these standardised definitions might lead to overdiagnosis of pneumonia, they are widely used globally for diagnosis and management, and enable comparison with data from other regions.

Study staff were trained and assessed in application of these case definitions and strong pneumonia surveillance systems were established. Although study nurses monitored every illness episode in birth cohort participants, some pneumonia events could have been missed. The participants who were lost to follow up might have had pneumonia events that were not reported to the study team; however, because these participants comprised only 2% of the cohort, such events are unlikely to have substantially affected the results. The chances that events warranting hospital admission were missed are low because Paarl Hospital is the only public hospital in the area; however, some ambulatory events could have been undercounted if mothers did not seek care. The incidence of pneumonia episodes might therefore represent the minimum incidence of pneumonia in this cohort.

These results might have low generalisability to other regions in Africa. However, this study was done in two heterogeneous communities, with meticulous measurement of a wide range of risk factors, allowing for wider generalisability to regions with similar distributions of risk factors. Furthermore, subgroup incidence estimates can be used to guide modelling of disease burden in regions with different prevalences of risk factors.

This is the first birth cohort study in a low-income to middle-income setting with a well established primary health-care system and an immunisation programme including new conjugate vaccines (panel). Prevention of childhood pneumonia through public health interventions addressing cessation of maternal smoking, prevention of HIV transmission, promotion of breastfeeding, child nutrition, and timely vaccination should be strengthened. To complement these findings, incidence estimations after the age of 1 year, and investigation of the infectious cause of childhood pneumonia in the context of high coverage of conjugate vaccination, should be prioritised for future research.

Panel: Research in context

Systematic review

We searched PubMed for articles published in English up to August, 2013, with the search terms "child" AND "pneumonia". We identified some high quality systematic reviews of the incidence and global burden of childhood pneumonia. However, the published evidence relied mainly on modelled estimates of pneumonia incidence or extrapolation from child mortality statistics. Accurate longitudinal data are scarce for the incidence of pneumonia in children and for severity of disease, especially after introduction of childhood pneumococcal conjugate vaccine in low-income and middle-income countries.

Interpretation

This study is one of the first birth cohort studies to longitudinally investigate the incidence, severity, and risk factors for childhood pneumonia in a low-income to middle-income setting after introduction of new conjugate vaccines. We noted a high incidence of pneumonia, with a high proportion of severe pneumonia cases in the first year of life. Exposure to environmental tobacco smoke, young age, male sex, and maternal HIV infection were associated with pneumonia or severe pneumonia. Childhood pneumonia remains an important public health problem despite the introduction of new conjugate vaccines. Attention to the broad determinants of childhood pneumonia is needed to prevent this disease burden.

Contributors

HJZ is the principal investigator, and conceived and designed the study, and obtained funding, together with MPN, the lead microbiologist, and LM, who led the epidemiological analyses. HJZ, MPN, and LM provided operational oversight. DMlR was the study clinician and coordinator, analysed preliminary data with supervision from LM, and was the main investigator responsible for interpretation of results and drafting of the manuscript. All authors reviewed, contributed to, and approved the final manuscript.

Declaration of interests

We declare no competing interests.

Acknowledgments

This study was funded by the Bill & Melinda Gates Foundation (grant number OPP 1017641), the South African Thoracic Society, the Federation of Infectious Diseases Societies of South Africa, and the University of Cape Town (PhD research associateship to DMlR). We thank the study staff; the clinical and administrative staff of the Western Cape Government Health Department at Paarl Hospital and at the clinics for support of the study; members of the study International Advisory Board for their advice; our collaborators; and the families and children who participated in the study.

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